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(54) Controlled release gastroresistant pharmaceutical formulations for oral administration containing bile acids and their salts.

(57) Controlled release pharmaceutical formulations for oral administration coated by an enterosoluble gastroresistant film, preferably selected from gastroresistant granulates, gastroresistant tablets, gastroresistant hard gelatine capsules containing powders or granulates or two or more tablets or oily suspensions, gastroresistant soft gelatine capsules containing oily suspensions and hard gelatine capsules containing gastroresistant granulates or two or more gastroresistant tablets, containing therapeutically effective amounts of a mixture of bile acids and their salts with alkali metals or organic bases, process for their preparation and therapeutic use thereof in the treatment of biliary calculoses, biliary dyspepsias, biliary cirrhosis and chronic and cholestatic hepatopathies.

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BACKGROUND OF THE INVENTION

The therapeutic activities of some bile acids like, for instance, ursodeoxycholic, chenodeoxycholic, cholic and deoxycholic acids are well known for some time. In a first time their use has been addressed to the dissolution of the cholesterol gall-stones, by virtue of their ability of inhibiting the cholesterol synthesis, helping the cholesterol removal through the formation of mixed micelles and inhibiting the cholesterol absorption in the intestine. Subsequently the bile acids were used to treat biliary dyspepsias, biliary cirrhosis and chronic and cholestatic hepatopathies, as described in Digestive Diseases 8, (1), 12-22, (1990) by Leuschner U. and Kurz W..

The oral therapy with bile acids is till now carried out by means of the administration of the acids in form of immediate or delayed release tablets or capsules. All these formulations show the drawback of giving an incomplete absorption, due to a scarce bioavailability as clearly shown by Parquet M. et al., European Journal of Clinical Investigation 15, (4), 171-8, (1985), Igimi H., Corey M.C., J. Lip. Res., 21, 72-90, (1980) and Roda A., Fini A., Hepatology, 4, 72-6, (1984).

This scarce bioavailability is due to the fact that bile acids, particularly ursodeoxycholic acid, dissolve very slowly in the intestine after having crossed unabsorbed and undissolved the stomach.

The water solubility of free bile acids, mainly that of ursodeoxycholic acid, is very low (53 μM) and, because of its restrained detergence (CMC = 14 mM), its solubility little raises with the increase of the pH and the complete solubilization takes place only at pH 8.47.

Therefore, ursodeoxycholic acid is completely solubilized and absorbed only when the intestinal pH exceeds the value of 8.4, while at lower values of pH a portion of ursodeoxycholic acid is not absorbed and undergoes a biotransformation to litocholic acid by means of the intestinal bacterial flora.

Therefore it is easily understandable why delayed release formulations containing ursodeoxycholic acid actually can have a lesser bioavailability than that of immediate release formulations in case the delayed release takes place in the intestinal zones where a greater metabolization contemporaneously occurs together with a greater solubilization.

Overcoming the problems of scarce absorption of the immediate or delayed release formulations containing bile acids used at present, is the aim of the present invention. This scope is obtained by means of enterosoluble gastroresistant pharmaceutical formulations containing a mixture of bile acids and their salts with alkali metals or organic bases.

The pharmaceutical formulations must be gastroresistant, because otherwise the strongly acid gastric juices would release the bile acids from their salts so that there would be again the problem of the slow and incomplete intestinal solubilization of the acids themselves.

The pharmaceutical formulations object of the present invention represent a significant improvement in comparison with prior art because they assure a remarkable increase in active principle absorption and at the same time they allow a modulation of active principle release.

This modulation depends on both salified fraction of active principle, which is immediately solubilized and absorbed, and non-salified fraction, which is solubilized and absorbed more slowly, and it concerns with both the maximum plasma concentration (C max) of active principle and the time in which said maximum concentration is obtained (T max). The therapeutic goals consisting in an increase of the maximum plasmatic concentration (C max) and a quicker achievment of said concentration (T max) together with a better total bioavailability, are achieved by the pharmaceutical formulations object of the present invention as it is clearly shown by biological tests of bioavailability carried out on men, by using a pharmaceutical formulation prepared according to the present invention in comparison with a commercial pharmaceutical formulation of ursodeoxycholic acid.

The experimental results showed a remarkable increase of the bioavailability of the formulation prepared according to the present invention in comparison with the commercial formulation. The average increase of the bioavailability (AUC) is equal to about 30%. Moreover the maximum hematic concentration (C max) reaches average values that are more than twice higher and a quicker achievement of the maximum hematic peak (T max) is also noticed; in fact the formulation according to the present invention reached this peak in about 3 and half hours on the average while the commercial formulation reached it in about 4 hours and half.

These experimental data on men clearly show the full achievement of the goals of the invention and therefore the pharmaceutical formulations object of the present invention are perfectly suitable for the therapeutic uses of bile acids, mainly for the treatment of biliary calculoses. biliary dyspepsias, biliary cirrhosis and chronic and cholestatic hepatopathies.

DETAILED DESCRIPTION OF THE INVENTION

Controlled release pharmaceutical formulations for oral use coated by an enterosoluble gastroresistant film containing therapeutically effective amounts of a mixture of bile acids and their salts with alkali metals or organic bases are the object of the present invention.

The process for preparing said pharmaceutical formulations and their therapeutic use in the treatment of biliary calculoses, biliary dyspepsias, biliary cirrhosis and chronic and cholestatic hepatopathies are further objects of the present invention.

Every kind of gastroresistant pharmaceutical formulations for oral use is suitable for the fulfillment of the present invention. Gastroresistant granulates, gastroresistant tablets, gastroresistant hard gelatine capsules containing powders or granulates or two or more tablets or oily suspensions, gastroresistant soft gelatine capsules containing oily suspensions and hard gelatine capsules containing gastroresistant granulates or two or more gastroresistant tablets, containing therapeutically effective amounts of a mixture of bile acids and their salts with alkali metals or organic bases, are the preferred forms.

The distinctive feature of these pharmaceutical formulations resides in that they are coated by an enterosoluble gastroresistant film which allows the salts of bile acids to cross the gastric juices unaltered and to be dissolved in the intestine where the absorption takes place. These pharmaceutical formulations contain an amount of bile acids in salified and non-salified form comprised between 50 and 750 mg and can be administered one or more times a day depending on the dosages and the individual therapeutic needs.

The ponderal ratios between the amount of bile acid and that of salt of bile acid in the pharmaceutical formulations object of this invention can be various.

Mixtures containing from 50% to 80% by weight of the salt of bile acid and from 20% to 50% by weight of bile acid are preferred in the realization of the present invention.

Moreover said mixtures can be made not only by a bile acid and its salt but also by a bile acid and a salt of another bile acid. For instance, a mixture can be composed of chenodeoxycholic acid and of the sodium salt of the ursodeoxycholic acid.

All the bile acids endowed with therapeutic activity can be advantageously used in the fulfillment of the present invention.

The cholic, deoxycholic, chenodeoxycholic, iocholic, iodeoxycholic and ursodeoxycholic acids are preferred in the realization of the present invention.

All the salts of the bile acids that show an adequate degree of solubility in aqueous medium or in a medium that simulates the intestinal fluid can be advantageously used in carrying out the present invention. The salts of the bile acids with alkali metals and with organic bases are preferred because of their solubility features. The salts of sodium, lithium, potassium, of tertiary aliphatic amines, like triethylamine, triethanolamine and trimethanolamine, of heterocyclic amines, like N-methylpiperidine, piperazine, morpholine, N-methyl-morpholine and 1-(2-hydroxyethyl)pyrrolidine, of basic aminoacids like L-arginine, L-lysine and L-ornithine, of aminosugars like D-glucamine, N-methyl-D-glucamine and glucosamine and of quaternary ammonium derivatives like choline are preferred among them.

All the enterosoluble gastroresistant pharmaceutical formulations for oral use can be advantageously used in the realization of the present invention. The preferred formulations are the gastroresistant tablets, the gastroresistant, both hard and soft, capsules and the capsules containing two or more gastroresistant tablets. In this last case the gastroresistant film can be different for each kind of tablet so that each tablet can be solubilized in a different tract of the intestine in order to greatly aid the absorption of the drug.

Gastroresistant coatings that can be solubilized at pH values respectively higher than 5, 6 and 7, so that the solubilization takes place in an aimed way, were selected for carrying out the present invention.

The non-coated pharmaceutical forms are prepared according to known methods by using normal excipients, for instance binding agents like polyvinylpyrrolidone, carboxymethylcellulose, microgranular cellulose, lactose, saccharose or mannitol, disintegrating agents like reticulated polyvinylpyrrolidone, starches, sodium starch glycolate or alginates, lubricating agents like talc, magnesium stearate or stearic acid.

The non-coated pharmaceutical forms obtained according to known methods are transformed into the enterosoluble gastroresistant pharmaceutical formulations object of the present invention by means of a double coating.

The first coating, which is not protective, is carried out by using hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide, talc and, optionally, pharmaceutically acceptable dyestuffs like, for instance, the iron oxides. This coating creates a film which acts as support for obtaining an optimal setting of the subsequent enterosoluble gastroresistant protective film on the pharmaceutical form. Many coating substances can be advantageously used to obtain an enterosoluble gastroresistant coating. Cellulose acetate, the copolymers of the methacrylic acid and of the methacrylic esters in different ratios, commercially known under the trade-mark EUDRAGIT ®, mainly EUDRAGIT ® L and EUDRAGIT ® S, polyvinylacetophthalate and hydroxypropylmethylcellulose phthalate.

Plasticizers, in an amount comprised between 5% and 15% in weight with respect to the amount of coating agent, are added for granting optimal flexibility and elasticity to the gastroresistant film.

Diethylphthalate, dibutylphthalate, triacetin, polyethylene glycols and acetylated monoglycerides are the plasticizers preferred in the realization of the present invention.

The process for preparing the pharmaceutical formulations object of the present invention comprises preparing according to known methods the various pharmaceutical forms for oral use not coated by the protective film. For instance the tablets are prepared by dry granulating the mixture of a bile acid and a bile acid salt, by mixing it with the normal excipients like, for instance, reticulated polyvinylpyrrolidone, microgranular cellulose, magnesium stearate and talc and tabletting the resulting mixture.

The hard gelatine capsules can be filled either with a powder made by the sole active principles or by a mixture of active principles together with one or more excipients, either with a granulate containing active principles alone or together with one or more excipients, or with a suspension of active principles in a suitable dispersing agent.

Afterwards the capsules are sealed, for instance, with an aqueous or hydroalcoholic solution of gelatine. The soft gelatine capsules can be filled with a

suspension of active principles in a suitable dispersing agent and then they are sealed.

The tablets or the capsules, so obtained by means of known methods, are then submitted to the gastroprotection. A first, non-protective, coating, useful as support for obtaining an optimal setting of the protective enterosoluble gastroresistant film on the pharmaceutical form, is carried out before executing the coating by means of the enterosoluble gastroresistant film.

This non-protective coating is carried out by sprying on the pharmaceutical forms in coating pan a suspension made by hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide, talc and, optionally, pharmaceutically acceptable dyestuffs like, for instance, the iron oxides, in a 22:1 mixture of ethyl alcohol and water. The weight of this first film is comprised between 1% and 5% of the weight of the non-coated pharmaceutical form.

The application of the enterosoluble gastroresistant film is carried out by solubilizing one or more coating substances together with one or more plasticizers in a solvent selected from methyl, ethyl or isopropyl alcohol, acetone or mixtures thereof with water and sprying this solution in coating pan on the pharmaceutical formulations previoulsy coated by means of the non-protective coating, in such an amount that the weight of the enterosoluble gastroresistant film is comprised between 2% and 10% with respect to the weight of the non-coated pharmaceutical form.

The so obtained enterosoluble gastroresistant pharmaceutical formulations are able to release the mixture of bile acids and their salts in the intestine allowing a rapid absorption of the bile acid salt and a delayed absorption of the non-salified bile acid in order to achieve the expected controlled release of the drug.

The positive results obtained with the formulations object of the present invention in comparison with prior art formulations are clearly shown by the experimental results of a pharmacokinetic test carried out on men.

One gastroresistant tablet according to the present invention, containing 237.6 mg of sodium salt of ursodeoxycholic acid and 225 mg of ursodeoxycholic acid prepared according to the method described in example 1, was administered to each of 6 healthy subjects, having a normal body weight, fasting for 8 hours. One week later the same persons were given, under the same circumstances, a tablet coming from a commercial pharmaceutical formulation containing 450 mg of ursodeoxycholic acid.

The hematic levels of ursodeoxycholic acid were evaluated for a period of time of 8 hours starting from the administration of the drug. They were evaluated by means of an immunoenzymatic method that uses specific antibodies for the free ursodeoxycholic acid prepared in New Zealand rabbits as described in articles of Roda A. et al. in Talanta, 31, 895, (1984) and in Analytical Biochemistry, 156, (2). 267-73, (1986).

The experimental results of the absorption during 8 hours, expressed as the area contained under the hematic curve (AUC), calculated as µmoles/l/8h, as the maximum hematic concentration that has been obtained (C max), expressed as µmoles/l, and as the time, expressed as hours, in which said maximum concentration has been obtained after the administration of the drug (T max), are reported in table 1.

TABLE 1

ABSORPTION TEST IN MAN

	Ursodeoxycholic acid and sodium salt of ursodeoxycholic acid according to Example 1			Commercial formulation of ursodeoxycholic acid		
Person	AUC (μmoles/l/8h)	Cmax (μmoles/l)	Tmax (h)	AUC (μmoles/l/8h)	Cmax (μmoles/l)	Tmax (h)
1	43.8	15.2	3.6	39.4	8	3.6
2	39.4	12.6	4.1	26.2	7	4.4
3	43.6	18.4	3.5	31.4	4.8	4.2
4	43.3	20.3	2.9	33.4	8.2	4.8
5	34.5	16.4	3.4	28.4	3.9	3.2
6	40.2	18.5	3.7	26.5	4.6	5.8
	$\bar{x}$ ±s.d.	$\bar{x}$ ±s.d.	$\bar{x}$ ±s.d.	$\bar{x}$ ±s.d.	$\bar{x}$ ±s.d.	$\bar{x}$ ±s.d.
	40.80±3.29	16.90±2.52	3.53±0.36	30.88±4.59	6.08±1.71	4.33±0.84

The experimental data reported in table 1 show that the absorption in man (expressed as AUC), by administering the same amount of the active principle, i.e. of ursodeoxycholic acid, increases of a value of about 30% for the pharmaceutical formulation according to example 1 in comparison with the commercial pharmaceutical formulation. Moreover the maximum hematic concentrations (C max) reached after the administration of the formulation described in example 1 are on the average twice higher than the maximum hematic concentrations reached after the administration of the commercial formulation. Lastly, also the speed of absorption is higher, because the reaching of the maximum hematic peak (T max) occurs, on the average, after about 3 and half hours after the treatment with the formulation according to example 1, i.e. about 1 hour before this reaching occurs with the commercial formulation of ursodeoxycholic acid.

Therefore the aim of the present invention of producing oral pharmaceutical formulations containing a bile acid as active principle and endowed with a better bioavallability in comparison with the pharmaceutical forms at present used, has been fully achieved.

Said oral gastroresistant pharmaceutical forms contain therapeutically effective amounts of a mixture of bile acids and their salts with alkali metals or organic bases, preferably comprised between 50 and 750 mg. and can be administered one or more times a day, depending on the dosages and the individual therapeutic needs, in the treatment of biliary calculoses, biliary dyspepsias, biliary cirrhosis and chronic and cholestatic hepatopathies.

The examples reported have to be considered only as a further illustration and not as a limitation of the invention.

EXAMPLE 1

Gastroresistant tablets containing the sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid

Composition of each tablet

- Sodium salt of the ursodeoxycholic acid	237.6 mg
- Ursodeoxycholic acid	225 "
- Reticulated polyvinylpyrrolidone	21 "
- Microgranular cellulose	210 "
- Magnesium stearate	12 "
- Talc	6 "
- Hydroxypropylmethylcellulose	14 "
- Polyethylene glycol 6000	0.4 "
- Titanium dioxide	3.2 "
- Talc	3.2 "
- Hydroxypropylmethylcellulose phthalate	32 "
- Acetylated monoglycerides	3.2 "

The mixture containing the sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid is dry compacted and granulated on a 0.8 mm sieve. The granulate is mixed for 15 minutes with reticulated polyvinylpyrrolidone, microgranular cellulose, magnesium stearate and talc and then the mixture is tabletted. The tablets are coated in coating pan first with a dispersion of hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide and talc in a 22:1 mixture of ethyl alcohol and water and then with a solution of hydroxypropylmethylcellulose phthalate and acetylated monoglycerides in a 89:11 mixture of ethyl alcohol and water.

EXAMPLE 2

Gastroresistant tablets containing the sodium salt of the chenodeoxycholic acid and chenodeoxycholic acid

Composition of each tablet

- Sodium salt of the chenodeoxycholic acid	237.6 mg
- Chenodeoxycholic acid	225 "
- Reticulated polyvinylpyrrolidone	21 "
- Microgranular cellulose	210 "
- Magnesium stearate	12 "
- Talc	6 "
- Hydroxypropylmethylcellulose	14 "
- Polyethylene glycol 6000	0.4 "
- Titanium dioxide	3.2 "
- Talc	3.2 "
- Hydroxypropylmethylcellulose phthalate	32 mg
- Acetylated monoglycerides	3.2 "

The tablets are prepared and coated according to the manner described in example 1.

EXAMPLE 3

Gastroresistant tablets containing the 1-(2-hydroxyethyl)pyrrolidine salt of the ursodeoxycholic acid and ursodeoxycholic acid

Composition of each tablet

- 1-(2-Hydroxyethyl)pyrrolidine salt of the ursodeoxycholic acid	225	mg
- Ursodeoxycholic acid	225	"
- Reticulated polyvinylpyrrolidone	21	"
- Microgranular cellulose	210	mg
- Magnesium stearate	12	"
- Talc	6	"
- Hydroxypropylmethylcellulose	14	"
- Polyethylene glycol 6000	0.4	"
- Titanium dioxide	3.2	"
- Talc	3.2	"
- Hydroxypropylmethylcellulose phthalate	32	"
- Acetylated monoglycerides	3.2	"

The tablets are prepared and coated according to the manner described in example 1.

EXAMPLE 4

Gastroresistant tablets containing the sodium salt of the ursodeoxycholic acid and chenodeoxycholic acid

Composition of each tablet

- Sodium salt of ursodeoxycholic acid	250	mg
- Chenodeoxycholic acid	200	"
- Reticulated polyvinylpyrrolidone	21	"
- Microgranular cellulose	210	"
- Magnesium stearate	12	"
- Talc	6	"
- Hydroxypropylmethylcellulose	14	"
- Polyethylene glycol 6000	0.4	"
- Titanium dioxide	3.2	mg
- Talc	3.2	"
- Hydroxypropylmethylcellulose phthalate	32	"
- Acetylated monoglycerides	3.2	"

The tablets are prepared and coated according to the manner described in example 1.

EXAMPLE 5

Gastroresistant tablets containing the sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid

Composition of each tablet

- Sodium salt of the ursodeoxycholic acid	125	mg
- Ursodeoxycholic acid	100	"

- Reticulated polyvinylpyrrolidone	10	mg
- Microgranular cellulose	100	"
- Magnesium stearate	6	"
- Talc	3	"
- Hydroxypropylmethylcellulose	7	"
- Polyethylene glycol 6000	0.2	"
- Titanium dioxide	1.6	"
- Talc	1.6	"
- Hydroxypropylmethylcellulose phthalate	16	"
- Acetylated monoglycerides	1.6	"

The tablets are prepared and coated according to the manner described in example 1.

EXAMPLE 6

Gastroresistant hard gelatine capsules containing the sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid

Composition of each capsule

- Sodium salt of the ursodeoxycholic acid	270	mg
- Ursodeoxycholic acid	180	"
- Reticulated polyvinylpyrrolidone	15	"
- Maize starch	10	"
- Magnesium stearate	10	"
- Talc	7	"
- Hydroxypropylmethylcellulose	5	"
- Polyethylene glycol 6000	0.2	mg
- Titanium dioxide	1.2	"
- Talc	1.2	"
- Eudragit ® L	20.7	"
- Dibutylphthalate	2	"

The sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid are mixed with the maize starch for 30 minutes and then the mixture is dry compacted and granulated on a 1 mm sieve. The granulate is mixed for 15 minutes with reticulated polyvinylpyrrolidone, magnesium stearate and talc and the mixture is shared in hard gelatine capsules that are sealed with a 31% (w/v) aqueous solution of gelatine. Subsequently the capsules are coated in coating pan first with a dispersion of hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide and talc in a 22:1 mixture of ethyl alcohol and water and then with a solution of Eudragit ®L and dibutylphthalate in isopropyl alcohol.

EXAMPLE 7

Gastroresistant capsules of soft gelatine containing the sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid

Composition of each capsule

- Sodium salt of the ursodeoxycholic acid	175 mg
- Ursodeoxycholic acid	50 "
- Precipitated silica	3 mg
- Caprilo-capric glycerides	450 "
- Hydroxypropylmethylcellulose	10.5 "
- Polyethylene glycol 6000	0.6 "
- Titanium dioxide	2.4 "
- Talc	2.4 "
- Hydroxypropylmethylcellulose phthalate	24 "
- Acetylated monoglycerides	2.4 "

A mixture of sodium salt of the ursodeoxycholic acid, ursodeoxycholic acid, precipitated silica and caprilo-capric glycerides is homogenized in a cylinder mill and then is shared in type 11 oval soft gelatine capsules. These capsules are first coated in coating pan with a first film made by a suspension of hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide and talc in a 22:1 mixture of 95% ethyl alcohol and water. Subsequently an enterosoluble gastroresistant coating is carried out by spraying in coating pan a solution of hydroxypropylmethylcellulose phthalate and acetylated monoglycerides in a 80:1 mixture of ethyl alcohol and water on the capsules coated with the first film.

EXAMPLE 8

Hard gelatine capsules containing the sodium salt of the ursodeoxycholic acid and ursodeoxycholic acid

- Sodium salt of the ursodeoxycholic acid	360 mg

- Ursodeoxycholic acid	90	mg
- Reticulated polyvinylpyrrolidone	15	"
- Microgranular cellulose	5	"
- Magnesium stearate	4	"
- Talc	2	"
- Hydroxypropylmethylcellulose	5	"
- Polyethylene glycol 6000	0.2	"
- Titanium dioxide	1.2	"
- Talc	1.2	"
- Eudragit ® L	20.7	"
- Dibutylphthalate	2	"

The sodium salt of the ursodeoxycholic acid and the ursodeoxycholic acid are mixed together and the so obtained mixture is dry compacted and granulated on a 0.8 mm sieve. The granulate is mixed for 15 minutes with reticulated polyvinylpyrrolidone, microgranular cellulose, magnesium stearate and talc and then the mixture is shared in hard gelatine capsules which are sealed and made gastroresistant according to the manner described in example 6.

EXAMPLE 9

Hard gelatine capsules containing gastroresistant tablets of sodium salt of the chenodeoxycholic acid and chenodeoxycholic acid

Composition of each non-protected tablet containing the sodium salt of the chenodeoxycholic acid

- Sodium salt of the chenodeoxycholic acid	100	mg
- Reticulated polyvinylpyrrolidone	5	"
- Microgranular cellulose	35	"
- Magnesium stearate	3	"
- Talc	1.5	"

Composition of each non-protected tablet containing chenodeoxycholic acid

- Chenodeoxycholic acid	100	mg
- Reticulated polyvinylpyrrolidone	5	"
- Microgranular cellulose	35	"
- Magnesium stearate	3	"
- Talc	1.5	"

The tablets are prepared by dry compacting and granulating the active principle on a 0.8 mm sieve. The granulate is mixed for 15 minutes with reticulated polyvinylpyrrolidone, microgranular cellulose, magnesium stearate and talc and then the mixture is tabletted. The obtained tablets are submitted to gastroprotection.

Coating of each tablet of chenodeoxycholic acid

- Hydroxypropylmethylcellulose	3	mg
- Polyethylene glycol 6000	0.1	mg
- Titanium dioxide	0.7	"
- Talc	0.7	"
- Hydroxypropylmethylcellulose phthalate	7	"
- Acetylated monoglycerides	0.7	"

The tablets are coated in coating pan first with a dispersion of hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide and talc in a 22:1 mixture of ethyl alcohol and water and then with a solution of hydroxypropylmethylcellulose phthalate and acetylated monoglycerides in a 89:11 mixture of ethyl alcohol and water.

The gastroprotected tablets are solubilized at a pH value higher than 5.

Coating of each tablet of the sodium salt of the chenodeoxycholic acid

- Hydroxypropylmethylcellulose	3	mg
- Polyethylene glycol 6000	0.1	"
- Titanium dioxide	0.7	"
- Talc	0.7	"
- Red iron oxide	0.4	"
- Eudragit® S	7	"
- Dibutylphthalate	0.7	"

The tablets are coated in coating pan first with a dispersion of hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide, talc and red iron oxide in a 22:1 mixture of ethyl alcohol and water and then with a solution of Eudragit^{R} S and dibutylphthalate in isopropyl alcohol. The gastroresistant tablets are solubilized at a pH value higher than 7.

The hard gelatine capsules are then filled with a tablet containing chenodeoxycholic acid and a tablet containing the sodium salt of the chenodeoxycholic acid.

Claims

1. Controlled release pharmaceutical formulations for oral use coated by an enterosoluble gastroresistant film containing therapeutically effective amounts of a mixture of bile acids and their salts with alkali metals or organic bases.

2. Pharmaceutical formulations according to claim 1 characterized in that they are selected from gastroresistant granulates, gastroresistant tablets, gastroresistant hard gelatine capsules containing powders or granulates or two or more tablets or oily suspensions, gastroresistant soft gelatine capsules containing oily suspensions and hard gelatine capsules containing gastroresistant granulates or two or more gastroresistant tablets.

3. Pharmaceutical formulations according to each of claims 1 and 2 characterized in that they contain from 50 to 750 mg of a mixture of bile acids and their salts with alkali metals or organic bases.

4. Pharmaceutical formulations according to claim 3 characterized in that in the mixture there are bile acids amounts comprised between 20% and 50% by weight and amounts of their salts comprised between 50% and 80% by weight.

5. Pharmaceutical formulations according to claim 1 characterized in that the bile acids are selected from cholic, deoxycholic, chenodeoxycholic, iocholic, iodeoxycholic and ursodeoxycholic acids.

6. Pharmaceutical formulations according to claim 1 characterized in that the salts of the bile acids are selected from the salts of sodium, lithium, potassium, triethylamine, triethanolamine, trimethanolamine, N-methylpiperidine, piperazine, morpholine, N-methylmorpholine, 1-(2-hydroxyethyl)pyrrolidine, L-arginine, L-lysine, L-ornithine, D-glucamine, N-methyl-D-glucamine, glucosamine and choline.

7. Pharmaceutical formulations according to each of claims 1 and 2 characterized in that the enterosoluble gastroresistant film is made by coating substances selected from cellulose acetate, copolymers of the methacrylic acid and of the methacrylic esters in different ratios, commercially known under the trademark Eudragit®, polyvinylacetophthalate and hydroxypropylmethylcellulose phthalate and by plasticizers selected from diethylphthalate, dibutylphthalate, triacetin, polyethylene glycols and acetylated monoglycerides and its weight is comprised between 2% and 10% of the weight of the non-coated pharmaceutical form.

8. Process for the production of pharmaceutical formulations according to claims from 1 to 7 which comprises coating the non-coated pharmaceutical forms prepared according to known methods with a first non-protective film by sprying in coating pan on said pharmaceutical forms a suspension made by hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide, talc and, optionally, pharmaceutically acceptable dyestuffs, in a 22:1 mixture of ethyl alcohol and water in such amount that the weight of this first film is comprised between 1% and 5% with respect to the weight of the non-coated pharmaceutical form, subsequently carrying out the coating with the enterosoluble gastroresistant film by sprying in coating pan on the pharmaceutical formulations a solution contalning one or more coating substances and one or more plasticizers solubilized in a solvent selected from methyl, ethyl or isopropyl alcohol, acetone or mixtures thereof with water, in such amount that the weight of the enterosoluble gastroresistant film is comprised between 2% and 10% with respect to the weight of the non-coated pharmaceutical form.

9. Use of the pharmaceutical formulations according to claims from 1 to 7 in the treatment of biliary calculoses, biliary dyspepsias, biliary cirrhosis and chronic and cholestatic hepatopaties.

Claims for the following Contracting State : ES

1. Process for the production of controlled release pharmaceutical formulations for oral use coated by an enterosoluble gastroresistant film containing therapeutically effective amounts of a mixture of bile acids and their salts with alkali metals or organic bases, which comprises coating the non-coated pharmaceutical forms prepared according to known methods with a first non-protective film by spraying in coating pan on said pharmaceutical forms a suspension made by hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide, talc and, optionally, pharmaceutically acceptable dyestuffs, in a 22:1 mixture of ethyl alcohol and water in such amount that the weight of this first film is comprised between 1% and 5% with respect to the weight of the non-coated pharmaceutical form, subsequently carrying out the coating with the enterosoluble gastroresistant film by spraying in coating pan on the pharmaceutical formulations a solution containing one or more coating substances and one or more plasticizers solubilized in a solvent selected from methyl, ethyl or isopropyl alcohol, acetone or mixtures thereof with water, in such amount that the weight of the enterosoluble gastroresistant film is comprised between 2% and 10% with respect to the weight of the non-coated pharmaceutical form.

2. A process according to claim 1, characterized in that pharmaceutical formulations are prepared which are selected from gastroresistant granulates, gastroresistant tablets, gastroresistant hard gelatine capsules containing powders or granulates or two or more tablets or oily suspensions, gastroresistant soft gelatine capsules containing oily suspensions and hard gelatine capsules containing gastroresistant granulates or two or more gastroresistant tablets.

3. A process according to each of claims 1 and 2, characterized in that pharmaceutical formulations are prepared which contain from 50 to 750 mg of a mixture of bile acids and their salts with alkali metals or organic bases.

4. A process according to claim 3, characterized in that pharmaceutical formulations are prepared in which in the mixture there are bile acids amounts comprised between 20% and 50% by weight and amounts of their salts comprised between 50% and 80% by weight.

5. A process according to claim 1, characterized in that pharmaceutical formulations are prepared in which the bile acids are selected from cholic, deoxycholic, chenodeoxycholic, iocholic, iodeoxycholic and ursodeoxycholic acids.

6. A process according to claim 1, characterized in that pharmaceutical formulations are prepared in which the salts of the bile acids are selected from the salts of sodium, lithium, potassium, triethylamine, triethanolamine, trimethanolamine, N-methylpiperidine, piperazine, morpholine, N-methylmorpholine, 1-(2-hydroxyethyl)pyrrolidine, L-arginine, L-lysine, L-ornithine, D-glucamine, N-methyl-D-glucamine, glucosamine and choline.

7. A process according to each of claims 1 and 2, characterized in that pharmaceutical formulations are prepared in which the enterosoluble gastroresistant film is made by coating substances selected from cellulose acetate, copolymers of the methacrylic acid and of the methacrylic esters in different ratios, commercially known under the trademark Eudragit® , polyvinylacetophthalate and hydroxypropylmethylcellulosephthalate and by plasticizers selected from diethylphthalate, dibutylphthalate, triacetin, polyethylene glycols and acetylated monoglycerides and its weight is comprised between 2% and 10% of the weight of the non-coated pharmaceutical form.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 5717

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 293 751 (INNOVA) * Claims *	1-9	A 61 K 31/575 A 61 K 9/28 A 61 K 9/48
A	GB-A-2 036 558 (LEHNER A.G.) * Whole document *	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16-06-1992	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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